GENETICS

Genetic variants associated with primary biliary cirrhosis

Variants of *HLA*, *IL12A* and *IL12RB2* are associated with primary biliary cirrhosis (PBC) according to the findings of a new study. The study findings also suggest alterations in interleukin 12 (IL-12) signaling may have a role in the pathogenesis of PBC. Lead researcher Katherine Siminovitch says their results are among the first to identify a set of functionally connected loci as being involved in the risk of disease. “These findings provide the first indication that IL-12 signaling may be causally relevant to PBC and identify modulation of this signaling pathway as a potential approach to therapy for PBC”, Siminovitch explains.

Epidemiologic data indicate that PBC has a genetic component; however, no validated biochemical or genetic markers can yet predict the outcome or course of this clinically heterogeneous disease. As Siminovitch notes, the shortcomings of

current approaches to PBC result in “...an urgent need for improved understanding of PBC pathogenesis that will enable prediction of risk and outcome, earlier diagnosis and treatment and more effective therapy for all PBC patients.”

To search for PBC-associated genes, the team performed a genome-wide association screen to genotype 536 patients with PBC and 1,536 controls for >300,000 single-nucleotide polymorphisms (SNPs). Multiple loci within the *HLA* class II region were associated with PBC, as were SNPs at the *IL12A* locus and the *IL12RB2* locus.

Although *HLA* class II alleles have been implicated in many autoimmune diseases, Siminovitch says that their data “provides an important confirmation of the relevance of *HLA* class II to PBC.” The *IL12A* and *IL12RB2* genes encode IL-12 α and IL-12 receptor β 2 proteins that

Credit: Kirsch, R. Mount Sinai Hospital, Toronto, ON, Canada

are involved in immunoregulation and inflammatory responses associated with autoimmune disease.

The researchers now plan to identify the precise alleles implicated in the pathogenesis of PBC in the hope that these genetic data can be used to predict disease risk and/or outcome.

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Original article Hirschfield, G. M. *et al.* Primary biliary cirrhosis associated with *HLA*, *IL12A*, and *IL12RB2* variants. *N. Engl. J. Med.* **360**, 2544–2555 (2009).